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Cardiac Dysfunction in Pediatric Oncology Patients with Severe Sepsis and Septic Shock: Retrospective Single Center Study

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Abstract

Objectives: To determine the prevalence of sepsis-induced cardiac dysfunction (septic cardiomyopathy) in pediatric oncology patients admitted to PICU, and to compare them to other oncology patients with sepsis/septic shock who have no cardiac dysfunction regarding the risk of mortality, average length of stay, duration of inotropic/vasopressor support, ventilation free days, and the need for renal replacement therapy.

Design: a retrospective analysis of Sixty-six pediatric patients with underlying oncology disease who were admitted to the Pediatric critical care unit at King Fahad Specialist Hospital with the diagnosis of sepsis or septic shock between January 2014 and December 2015. Severe sepsis and septic shock were defined based on the definition of the Surviving Sepsis Campaign 2012. Sepsis-related cardiac systolic dysfunction (septic cardiomyopathy) was defined by High sensitive Troponin I, CK-MB and high BNP according to King Fahad Specialist Hospital-Dammam (KFSH-D) laboratory reference, Ejection fraction less than 50%, and shortening function less than 25% by transthoracic echocardiography, provided that transthoracic echocardiography is normal prior to PICU admission.

Results: The Prevalence of cardiac dysfunction in oncology patients having sepsis, severe sepsis or septic shock was 18.33%. (11 out of 60) (95% CI: 10.56, 29.92). The risk of mortality was higher in this group compared to those without cardiac dysfunction (54.5% versus 12.2%, p-value 0.005) regardless of the level of the cardiac enzymes (Troponin I, CK-MB and BNP). Oncology patients with cardiac dysfunction required more frequent mechanical ventilation, inotropic/vasopressor support and renal replacement therapy (p-value is 0.037, 0.031, and 0.001 respectively) but no significant increase in the length of stay or the duration of mechanical ventilation and inotropes (p-value 0.483, 0.068 and 0.105 respectively).

Conclusion: Sepsis-induced cardiac dysfunction in pediatric oncology patients is more liable to have a higher risk of mortality; they required more frequent inotropic/vasopressor support, renal replacement therapy, and mechanical ventilation. Randomized controlled trials are necessary to determine the optimal timing for diagnosis and management strategy in septic patients having cardiac dysfunction.

Keywords: Cardiac dysfunction; Sepsis; Septic shock; Pediatric; Oncology patient; Troponin I; CK-MB; BNP; Echocardiography; Ejection fraction; Shortening fraction

Introduction

Cardiac dysfunction is relatively common in oncology patients admitted to PICU with septic shock and severe sepsis that leads to a higher risk of morbidity and mortality. It has been reported in 31%-80% of patients with sepsis, septic shock and systemic inflammatory response syndrome (SIRS) [1]. Cardiac dysfunction in septic patients characterized by diminished contractility, impaired ventricular response to fluid therapy, and ventricular dilatation in some patients. Studies support a complex underlying pathophysiologic mechanism leading to myocardial depression in these patients [2]. Factors such as cytokines (TNF-α, IL-1β), endothelin-1, and lysozyme C directly inhibit myocyte contractility. While the role of Nitric oxide in septic cardiomyopathy is complicated [1-4]. Other studies have demonstrated that apoptosis and mitochondrial dysfunction play a role in the development of cardiac dysfunction in sepsis [2,5]. Although Elevation of troponins, BNP, and creatinine kinase (CK-MB) are seen frequently in the case of sepsis-related cardiac dysfunction, the mechanism for such troponin release, its clinical significance, and what management we should apply in such settings remain unclear [1].

Unlike adults who usually have a compensatory mechanism to maintain adequate cardiac output, children often exhibit a "low cardiac output" state secondary to severe myocardial depression. It has been reported that Multi-organ failure secondary to low cardiac output is the most common cause of mortality in children with sepsis rather than vasomotor paralysis [6]. According to sepsis surviving campaign, Fluid resuscitation is the first-line therapy for septic shock in children and those who are Fluid-refractory demand therapy to improve their myocardial dysfunction that continued despite the restoration of their preload. Clinical findings, laboratory values, and echocardiographic indices can guide the Initiation of the appropriate therapy aiming to maintain an adequate cardiac index [6].

Methods

This is a retrospective study conducted at King Fahad Specialist Hospital in Dammam, between January 2014 and December 2015. King Fahad Specialist Hospital is a tertiary referral hospital with a 400-bed capacity, 24 beds pediatric oncology ward, with an additional two beds

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for bone marrow transplant, and 12-bed pediatric oncology daycare services. Our pediatric critical care is a 10-bed Capacity unit, which provides both medical and surgical services, but no cardiac surgery. The study was approved by King Fahad specialist hospital Institutional Research Ethics Board (IRB).

All Oncology patients between the ages of 1 month to 16 years admitted to the PICU during the study period with the diagnosis of sepsis, severe sepsis, or septic shock were included in the study. Septic shock and severe sepsis were defined based on the definition of the Surviving Sepsis Campaign 2012 [1]. Sepsis as probable documented or suspected infection and signs of systemic inflammation. Severe sepsis as sepsis and organ dysfunction or tissue hypo-perfusion. And Septic shock defined as sepsis-induced shock or hypotension despite adequate fluid resuscitation.

Cardiac enzyme and a trans-thoracic echocardiogram were obtained in all eligible patients within 24-hours of admission and interpreted by a pediatric cardiologist. Cardiac systolic dysfunction was defined by, High sensitive Troponin I, CK-MB, high BNP, according to King Fahd specialist hospital Dammam laboratory references, And ejection fraction (EF) less than 50% with shortening function (SF) less than 25% using trans-thoracic echocardiography [4]. Any patient who is known to have previous cardiac disease or cardiac dysfunction (chemotherapy-related or non-related) with ejection fraction less than 50% and shortening fraction less than 25% confirmed by trans-thoracic echocardiogram before PICU admission were excluded.

All variables, including demographic data and patients characteristics needed to satisfy the objective of the study, had been collected. The data were extracted from the medical record, medical-plus electronic system and Echocardiography room by the co-investigators. Data tested for reliability by ensuring that the data is sufficiently complete, accurate, and error-free. Data were analyzed using an IBM personal computer with Statistical Package of Social Science (SPSS) version 20 and Epi Info 2000 programs.

Continuous variables reported in the form of median and interquartile range (IQR), while categorical variables presented in the form of numbers and percentages (%). Cross-tabulation and Fisher's exact test were used to compare the two groups for the categorical variables and Mann-Whitney U test for continuous variables (if not normally distributed). Fisher's exact test was used instead of chi-square because sample size in each cell is not meeting the requirement to achieve an accurate result. Both P-Value and 95% confidence intervals were calculated. P-value equal to or less than 0.05 were considered significant.

Results

Sixty-six oncology patients aged from one month to 16 years were enrolled during the study period between January 2014 and December 2015. Six patients were excluded as they have chemotherapy-related cardiac dysfunction. The Prevalence of cardiac dysfunction in pediatric oncology patients with sepsis, septic shock, and severe sepsis was estimated to be 18.33%. The demographic and clinical characteristics of the study cohort are presented in Table 1. The age of patients was ranging between 3.39-11.38 years with no statistical difference between the two groups.

Forty patients (66.67%) were diagnosed as hematological disorders (leukemia and lymphoma), 6 (10%) patients have brain tumors, and 14 (23.33%) have solid tumors. There were significant differences between the causes of PICU admission in both groups; all patients with septic cardiomyopathy (100%) were admitted with septic shock, while only 51.7% of the patients without cardiac dysfunction had septic shock. The remaining 26 (43.3%) of them were admitted with sepsis, and 5% with severe sepsis (p-value 0.001). The total dose of cardio-toxic medication

Baseline Characteristics	Cardiac Dysfunction	Normal Cardiac Function	Total No.	P-value
Age/year, Median(IQR)[b]	11.32(4.95 -1205)	7.17(2.72 – 11.12)	8.11(3.39 – 11.38)	0.086 ++
Gender, N (%)[a]				
Male	4(36.4)	22(44.9)	26(43.3)	0.742 +
Female	7(63.6)	27(55.1)	34(56.7)	
Primary Diagnosis, N (%)[a]				
Hematological tumors			40 (66.67)	
Brain tumors			6(10)	
Solid tumors			14(23.33)	
Causes of PICU Admission, N (%)[a]				
Sepsis	0(0)	26(53.1)	26(43.3)	0.001**
Sever sepsis	0(0)	3(6.1)	3(5)	
Septic shock	11(100)	20(40.8)	31(51.7)	
Blood Culture/Central, N (%)[a]				
Yes	3(27.3)	4(8.5)	7(21.1)	0.117 +
No	8(72.7)	43(91.5)	51(87.9)	
Total dose/mg per m^2, Median(IQR)[b]	109(9 - 200)	109(61.15 - 200)	109(56.72 - 200)	0.992 ++
Post BMT, N (%)[a]				
Yes	1(9.1)	5(102)	6(10)	1.0 +
No	10(90.9)	44(89.8)	54(90)	
P-value for comparing each variables between cardiac function status groups.				
*P-value ≤ 0.05, **p-value ≤ 0.01, ***p-value ≤ 0.001				
[a] Fisher's exact test was used to obtain the p-value.				
[b] Mann-Whitney U test was used to obtain p-value				

Table 1: Baseline characteristics.

(Anthra-cycliness) chemotherapy dose/m^2 was similar between the two groups, with a median of 109 (p-value 0.992). There was only one BMT patient (9.1%) in the cardiac dysfunction group and five patients (10.2%) in the other group with insignificant p-Value. The number of positive blood cultures was 3 (27.3%) in the first group and 4 (8.5%) (p-value=0.117), as shown in Table 1.

The study did not show any significant difference in PICU length of stay between the two groups (4 days, p-value 0.483) or the duration of mechanical ventilation with a median of 4 days compared to 5 days in the other group (P. value 0.93), (Table 2). However, patients with septic cardiomyopathy need more frequent mechanical ventilation 10 (90.9%) compared to 26 (53.1%) in the group without cardiac dysfunction (p. value 0.037).

There is a frequent need for renal replacement therapy (RRT) in patients with septic cardiomyopathy 18.2% while none of the patients in the other group required RRT (P-value 0.031). Patients with septic cardiomyopathy also required more inotropic /vasopressor support, eight patients in this group (72.7%) need more than two inotropic/ vasopressor drugs compared to only three patients from the other group (6.1%) (P-value <0.001). On the other hand, 27.3% of patients with septic cardiomyopathy require two or less than two inotropic support versus 93.9% in the other group. In spite of no statistical difference regarding the duration of inotropic/vasopressor support between both groups, median (IQR) 4 days Versus 3 days (P-Value 0.105) (Table 2).

The mortality risk was much higher in septic cardiomyopathy group of patients 54.5%(n=6 out of 11 patients) compared to 12.2% in patients without septic cardiomyopathy (p. value 0.005), (Table 2). This high mortality is associated with affection of shortening fraction (SF) (Shortening fraction, median 11.45 (10.7 - 23.15) in dead patients from septic cardiomyopathy versus 23.7 (18.86 - 25.1) in alive patients with septic cardiomyopathy (p. value 0.028) (Table 3). This association was not found either with the affection of ejection fraction (EF) median of 48.1 in dead patients compared to 27.15 in alive patients (P value 0.114) or with any of the cardiac markers (Troponin I median 79.2 Versus 890.85 (P. Value 0.1), CK MB (median 1.5 versus 18.25 (P-Value 0.068) and BNP median 1718 versus 7191 (P. Value 0.201) (Table 3).

Five patients with sepsis-related cardiomyopathy discharged from PICU and hospital. Two of them were started on Captopril and furosemide by a cardiologist as they have residual LV dysfunction. Follow up transthoracic echocardiography over one year revealed improvement of cardiac dysfunction to normal when Captopril and furosemide weaned off. The other three patients passed away secondary to the aggressive primary tumors.

PICU Outcomes	Cardiac Dysfunction	Normal Cardiac Function	Total No.	p-value
Status, N (%)[a]				
Alive	5(45.5)	45(87.8)	48(80)	0.005**
Dead	6(45.5)	6(12.2)	12(20)	
Length of PICU Stay / Days, Median(IQR)[b]	4(2-12)	4(2-7.5)	4(2-8)	0.483 ++
Mechanical Ventilation, N (%)[a]				
Yes	10(90.9)	26(53.1)	36(60)	0.037*
No	1(9.1)	23(46.9)	24(40)	
Duration Of MV/Days , Median(IQR)[b]	4(2 -12)	5(3 - 9)	5(25 – 9.5)	0.93 ++
Use of CRRT, N (%)[a]				
Yes	2(18.2)	0(0)	2(3.3)	
No	9(81.8)	49(100)	58(96.7)	0.031 +
Number of Inotropics, N (%)[a]				
≤ 2	3(27.3)	46(93.9)	49(81.67)	<0.001 +
>2	8(72.7)	3(6.1)	11(18.33)	
Duration Of Inotropic Support/ Days, Median (IQR)	4(2-12)	3(1-4)	3(1 - 4.5)	0.105 ++
P-value for comparing each variables between cardiac function status groups. *P-value ≤ 0.05, **p-value ≤ 0.01, ***p-value ≤ 0.001 a Fisher's exact test was used to obtain the p-value. b Mann-Whitney U test was used to obtain p-value. MV= mechanical ventilation, CRRT= continuous renal replacement therapy.				

Table 2: PICU Outcomes.

Cardiac Markers on Picu Outcome	PICU Outcome		P -value
	ALIVE	DEAD	
Troponin I, Median (IQR)[b]	79.2(51-259)	890.85(75.45 – 2299.33)	0.1 ++
C K –MB, Median (IQR)[b]	1.5(0.39-8.78)	18.25(3.25 – 285.5)	0.068 ++
BNP, Median (IQR)[b]	1718(448.5 -1858.5)	7191(773.25 – 11811.25)	0.201 ++
Ejection Fraction, Median (IQR)[b]	48.1(35.41 – 49.35)	27.15(25.53 – 44.25)	0.114 ++
Shortening Fraction, Median (IQR)[b]	23.7(18.86 -25.1)	11.45(10.7 -23.15)	0.028*
P-value for comparing each variables between cardiac function status groups. *P-value ≤ 0.05, **p-value ≤ 0.01, ***p-value ≤ 0.001 a Fisher's exact test was used to obtain the p-value. b Mann-Whitney U test was used to obtain p-value.			

Table 3: Cardiac markers on PICU outcome.

Discussion

Septic myocardial dysfunction (SMD) during septic shock had been reported since 1984 by Raj et al. [7], but the prevalence, prognosis, and clinical significance are still not well understood. Cardiac dysfunction has a significant impact on the clinical outcomes of severe sepsis and septic shock. Cardiac dysfunction is not one clinical element; rather it is a spectrum of syndromes characterized by various pathophysiologic, microvascular, metabolic, anatomic, and functional abnormalities [1-3,7]. The prevalence of left ventricle (LV) systolic dysfunction during septic shock varies between studies (18-65%) [4,8] this can be explained by the timing of assessment, and the precision of the routine indices used to evaluate LV systolic function [7].

We enrolled Sixty-Six patients during the study period, and Cardiac dysfunction was detected in 18.33% of those patients who were admitted with sepsis and septic shock, which is lower compared to other studies. The fact that we combine elevated troponin I, BNP, CK-MB [8,9], and transthoracic Echocardiography indices of EF less than 50% and SF less than 25% to define the systolic cardiac dysfunction [2] while diastolic dysfunction was not included, might be contributing to this results. Prabhu et al. reported 9.1% isolated systolic dysfunction in the ICU patients [10], While Boissier et al. found that the prevalence of LV systolic and or diastolic dysfunction to be 53%, [1,11]. Another study found the incidence of acute left ventricular dilation along with the reduction of EF to be 20-60% in patients with septic shock and was reversible among survivors [12,13]. Evaluation of systolic function based on left ventricular ejection fraction (LVEF) in Echocardiogram is misleading as the afterload in septic patients is remarkably reduced, and LVEF may be reported inaccurately as normal [9]. Additionally, Investigators defined myocardial dysfunction in the setting of sepsis using different echocardiographic cutoffs like derived LV longitudinal peak systolic strain that might be reduced earlier than LVEF deteriorated [1,7].

We reported a significant difference between both groups regarding the cause of PICU admission as all patients (100%) with septic cardiomyopathy were admitted with septic shock and only 51.7% (p-value 0.001) in the other group were admitted with septic shock (Table 1) despite the similarity between both groups demographically and clinically. Septic cardiomyopathy patients were severely sick as defined By (PRISM) or pediatric maximum SOFA (Sepsis-related Organ Failure Assessment) scores [14,15]. There was no significant difference between both groups regarding the length of PICU stay or the duration of mechanical ventilation. However, 90.9% of patients with septic cardiomyopathy required more frequent mechanical ventilation compared to 53.1% in the group without cardiac dysfunction. We contribute this to the severity of illness in patients with septic cardiomyopathy as all of them were in shock state upon admission to PICU. This finding is similar to a study conducted by Raj et al. [7,11] and opposite to what Tonial et al. had reported in his pilot study, where patients with cardiac dysfunction had longer PICU stay (p=0.020), hospital stay (p=0.047), maximum inotropic score (p=0.001), duration of mechanical ventilation (p=0.011), and fewer ventilator-free hours (p=0.020) [16].

In general, patients with septic cardiomyopathy patients were sick having multisystem organ failure (especially acute kidney injury), high PRISM score [14], (PSOFA) pediatric Sequential Organ Failure Assessment score [15] and they required more support by renal replacement therapy and inotropic/vasopressor support [17,18] as shown in our study. The septic cardiomyopathy group, 2 out of 11 (18.2%) patients needed RRT while none from the other group. In our unit we manage shock state by epinephrine +/- norepinephrine and if the patient has cardiomyopathy we add Milrinone or Dobutamine according to the clinical condition and individual experience of practice (Table 2).

Despite no differences regarding the duration of inotropic/vasopressor support between both groups. 72.7% of patients with septic cardiomyopathy required more than two inotropic/vasopressor compared to 6.1% of patients from the group without septic cardiomyopathy with significant p-value<0.001. This could be explained by the severity of illness of septic cardiomyopathy patients, high PRISM score, PSOFA, and the critical condition with shock state upon admission. Mehta et al. reported septic cardiomyopathy to be associated with an increased need for inotropic/vasopressor support, length of ICU stay, and adverse outcome in septic patients [17]. In some hospitals, mortality rates of pediatric septic shock are high, ranging between 18% and 50% and up to 60% in cardiogenic shock [19].

We reported a higher mortality rate in the septic cardiomyopathy group of 54.5% compared to 20% of patients from the other group (P-value 0.005) (Table 2). Haque et al. retrospectively studied 71 children (1 mo-16 year) over a two-year period that were admitted with fluid-refractory septic shock and concluded that children with high inotropic score are associated with a high mortality rate [20]. This might explain the high mortality of septic cardiomyopathy patients in our study as they required more than two inotropic/vasopressor (72.7%). A study was done by Raj et al. and found that the rate of mortality was 7% [7], which significantly lower than our study [11]. It has been found that the majority of patients with SIRS, sepsis, or septic shock had elevated troponin at the time of death [1,5]. This indicates that high troponin level is an independent risk factor for short- and long-term mortality in critically ill patients [18,20].

This is opposite to our study where there was no association between mortality rate and level of cardiac biomarkers (Troponin I, CK-MB, and BNP (p. value 0.1, 0.068 and 0.201, respectively) (Table 3). However, the increase in BNP levels in patients with severe sepsis or septic shock was correlated with the severity of illness rather than cardiac dysfunction, and failure of the BNP level to decline over the first few days was associated with higher mortality [21].

Similarly, the risk of mortality was not associated with the level of affection of ejection fraction (p-value 0.114) but associated significantly with the affection of shortening fraction (p-value 0.028) (Table 3). This may be because the shortening fraction is more sensitive than ejection fraction in the detection of cardiac dysfunction, or this may be statically false due to a small sample size. While in a prospective study conducted by Prabhu et al. who concluded that low ejection fraction was a predictor of mortality in patients with septic shock [10].

The limitation of our study is a retrospective and single-center study with a relatively small number of patients (total 60 and 11 with cardiac dysfunction). We did not include patients with sepsis other than oncology patients, as 60% of our admissions are pediatric oncology patients, and the most frequent cause of admission is febrile neutropenia, sepsis, and septic shock.

However, we think there is significant Clinical relevance of the study as it defined the magnitude of problems among critically ill pediatric patients with sepsis and septic shock in our institution. It also highlights the importance of early screening for cardiac dysfunction in a patient with septic shock and properly manages them in an appropriate time.

The long-term effect of septic shock with cardiac dysfunction treated with vasopressor/inotropic support is not known. Fenton et al. found a significant improvement in cardiac function in the majority of patients, and only 6% of patients had a rhythm disturbance with decreased ventricular function [22]. That is Similar to our patients with septic cardiomyopathy who recover completely in the follow-up echocardiogram.

Until recently, there are no clear guidelines regarding the proper time of screening and the best diagnostic modality of such patients [1]. Or consensus management approach regarding inotropic support is excited [1]. Gattinoni et al. treated critically ill patients with dopamine and Dobutamine intending to improve cardiac index above average values but, failed to reduce morbidity and mortality [23]. Others suggested adding Milrinone; however, its use to treat critically ill patients with impaired cardiac function can be neither recommended nor refuted [2,24,25]. This raises the suggestion for the future controlled trials of best early accurate diagnosis modality and management to enhance recovery and improve outcome.

Conclusion

Cardiac dysfunction secondary to sepsis (septic cardiomyopathy) is common among pediatric oncology patients with a high risk of mortality. They significantly need more frequent mechanical ventilation, renal replacement therapy, and (vasopressor-inotropic) support. To date, there is no clear recommendation regarding early accurate diagnosis and management of myocardial dysfunction in such patients. We suggest conducting further controlled trials aiming to enhance recovery and improve the outcome.

Ethical Approval

The Institution Review Board and ethics committee at King Fahd specialist hospital Dammam approved the study. No consent has been obtained from patients before the study as the data was collected retrospectively

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